REMARKS

The Invention

Applicants have discovered that stem cells in mammalian peripheral tissue containing sensory receptors are multipotent neural stem cells. These cells are capable of adopting cell fates not observed in the tissue from which they are found. Thus, the cells are useful, for example, for cell transplantation into the central nervous system of a mammal.

The Office Action

Claims 31-48 are pending. Claims 46 and 47 were rejected for lack of enablement. Claims 31-45 and 48 were rejected for anticipation or obviousness.

Support for the Amendments

In order to hasten allowance, Applicants now cancel claims 31, 34-37, 39, 40, and 48 without prejudice. New claim 49 has been added. Support for the new claims is found throughout the specification (see, for example, page 21, line 8, to page 22, line 21). No new matter has been entered by these amendments.

Rejections under 35 U.S.C. 112, first paragraph

Claims 46 and 47 stand rejected for lack of enablement. These claims are directed to pharmaceutical compositions that include the isolated neural stem cells of the present invention or cells differentiated from them. The Examiner states that the specification "does not teach the skilled artisan the manner in which to treat a neurodegenerative disorder by transplantation of isolated . . . precursor cells." Applicants respectfully traverse this rejection.

Burden to Establish Reasonable Basis to Question Enablement

As an initial matter, Applicants respectfully direct the Examiner's attention to M.P.E.P. § 2164.04, where it is stated that the Office has the initial burden for establishing a reasonable basis to question the enablement of the claimed invention. On this point, Applicants note that no evidence currently of record in this case establishes a basis for doubting the objective truth of the statements found in Applicants' specification regarding the transplantation of cells into the central nervous system (CNS) of a mammal. Instead, the Examiner asserts that the specification is not enabling because of "it would require undue experimentation for the skilled artisan to make and use the claimed invention." No evidence is provided to support this assertion of undue experimentation. By contrast, Applicants demonstrate, at page 28, line 24, to page 33, line 22 of the specification, transplantation of neurons differentiated from neural stem

cells isolated from the olfactory epithelium into the rat central nervous system.

The *Wands* Factors

The Examiner lists eight factors that are considered when determining whether claims are enabled by the specification: (i) breadth of the claims; (ii) nature of the invention; (iii) state of the prior art; (iv) the skill level of one in the art; (v) the level of predictability; (vi) the amount of direction provided by the specification; (vii) the presence of working examples; and (viii) the quantity of experimentation. Examination of these factors, generally referred to as the *Wands* factors (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988)), supports Applicants' position that the claims are enabled by the specification. The rejected claims are discussed below in view of each *Wands* factor.

Breadth of Claims

Claims 46 and 47 are directed to pharmaceutical compositions that include the isolated neural stem cells of the present invention or cells differentiated from them. These cells were discovered by Applicants as having previously unrecognized multipotency. This multipotency gives rise to pharmaceutical uses for these cells which were not previously recognized (e.g., cell transplantation for the treatment of neurological diseases and disorders). Accordingly, the claims are of a scope

commensurate with this discovery.

Nature of the Invention

As indicated in the previous paragraph, Applicants discovered that the cells described in the specification have unexpected desirable properties, namely (i) the ability to make cells other than those normally found in the peripheral tissue from which they were isolated (e.g., CNS neurons and glia), and (ii) the ability to expand the cell population in culture without loss of multipotency. These properties are desirable because a major limitation to the therapeutic practice of cell transplantation has been the lack of an adequate supply of cells (see, for example, Lindvall, Cell Transplant. 4:393-400, 1995, a copy of which is enclosed). Applicants demonstrated experimentally that the cells of the invention could be substituted for other cells in previously-established transplantation protocols (see below).

The State of the Prior Art and Skill of Practitioners in the Art

Both the state of the prior art and the skill of those in the art at the time of filing support Applicants' position that the claims are enabled by the specification. At the time of filing, the ability to (i) transplant CNS neurons and glia (or their cells from which CNS neurons or glia are derived) into the damaged brain of a mammal; (ii) have the cells survive; and (iii) at least partially restore function was routine. In one art example, a

rodent model for Parkinson's disease, dopaminergic neurons are selectively ablated by infusion of the neurotoxin 6-hydroxydopamine (6-OHDA). In this model, transplanted neurons are observed to survive, grow neurites, and form synapses, leading to reversal of behavioral deficits (see, for example, Zhou, Neurosci. Lett. 163:81-84, 1993; Nikkah et al., J. Neurosci. 14:3449-3461, 1994; Constantini et al., Exp. Neurol. 127:219-231, 1995; Nikkah et al., J. Neurosci. 15:3548-3561, 1995 (copies enclosed)). The positive results from these types of studies were responsible, in part, for justifying transplantation of fetal human tissue into the brains of humans suffering from Parkinson's disease. Again, functional improvement was observed (see, for example, Lindvall, *supra*; Kordower et al., J. Comp. Neurol. 370:203-230, 1996 (copies enclosed).

The foregoing results demonstrate that methods established using animal models in the field of cell transplantation are predictive of success in humans. In this regard, animal models for Huntington's disease and hereditary ataxia have also been used for assessment of cell transplantation therapy (see, for example, Zhang et al., Nature Med. 2:65-71, 1996; Pundt et al., Brain Res. Bull. 39:23-32, 1996 (copies enclosed)). In these models, the transplanted cells engrafted and, in at least one case, function was partially restored. One could reasonably predict, based on the findings described above, the successful treatment of human diseases other than Parkinson's disease with cell transplant therapy. The problem in the art of cell transplantation prior to Applicants' invention has been obtaining an adequate source of cells for transplantation, a problem

Applicants' invention solves.

The Amount of Direction in the Specification and the Presence of Working Examples

Two additional factors determine whether claims are enabled by the specification: the amount of direction in the specification and the presence of working examples. Applicants' specification clearly satisfies each of these factors. Applicants first describe methods for making the claimed compositions from the peripheral tissue of several species, including humans. Applicants further provide examples of the isolated neural stem cells themselves. Finally, Applicants demonstrate utility by administering the claimed compositions to an art-recognized animal model for Parkinson's disease, 6-OHDA-treated rats. In this working example, the cells survived and engrafted and expressed markers of dopaminergic neurons. Thus, Applicants' specification provides sufficient teaching regarding the use the neural stem cells in a pharmaceutical context.

Unpredictability in the Art

From the foregoing description of the state of the prior art and the working examples, Applicants submit that successful transplantation of cells into the central nervous system was predictable. At the time of filing, cells from a wide variety of sources had been transplanted into the central nervous system with success. Moreover,

Applicants provide specific examples describing the making and using of the claimed cells, including a working example in which cells, transplanted into the brain of a rat, were shown to survive and exhibit the desired phenotype *in vivo*. Thus, one in the art could combine the teachings of the specification with those in the art and practice the invention to its full scope. As is described in the art, the unpredictability in transplantation lies in the limited availability of cells and the host response to xenotransplantation (see the enclosed Declaration of Freda Miller, a named inventor in the present application). Applicants' discovery of multipotent neural stem cells that can be readily isolated from a person, expanded in culture, and then transplanted into the same person overcomes each of these obstacles to predictability.

Quantity of Experimentation

To make and use the claimed compositions requires only Applicants' teaching that neural stem cells can be isolated from peripheral tissue using the described method and standard techniques that were known to those skilled in the art at the time of the present invention. Such routine experimentation, namely the harvesting, culturing, and injection of cells, is routine and does not constitute undue experimentation (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988)). In sum, the required experimentation is routine and the art itself is predictable in nature. For these reasons, the rejection of claims 46 and 47 should be removed, and such action is respectfully requested.

New claim 49 addresses the Examiner's rejections

Applicants now enter new claim 49, directed to a neural stem cell produced according to the method of the invention and transplanted into the mammal from which the neural stem cell was derived. Applicants refer the Examiner to their comments regarding the enablement of claims 46 and 47; these comments are equally applicable to claim 49, and Applicants thus assert that claim 49 is enabled by the specification. The new claim is also novel over Sosnowski, Shubert, and Ronnett, as none of these references describes or suggests the claimed cell, nor is such a cell obvious over any combination of the cited references. While Sosnowski, at page 47, second column, suggested transplantation of cultured olfactory epithelium into the CNS, Sosnowski did not include the step of isolating neural stem cells: "The dissociated regenerating epithelium consisted of mitotically active neurons, supporting cells and basal cells." (page 45, second column). Moreover, Sosnowski only demonstrated the production of olfactory neurons, olfactory support cells, and the olfactory epithelium-specific basal stem cell, none of which had demonstrated use in a cell therapy method for the central nervous system. Accordingly, one in the art would not have predicted that transplantation of Sosnowski's regenerating olfactory epithelium would have any therapeutic success, and thus would not have been motivated to transplant a cell from the olfactory epithelium of a mammal into the CNS of that same mammal.

Applicants' finding of multipotent neural stem cells in peripheral tissue such as

olfactory epithelium was completely unexpected. None of the cited references recognized that the tissues under study (i.e., olfactory epithelium and tongue) contained a cell that was capable of making cell types other than those found in the olfactory epithelium or tongue, respectively. For the record, Applicants note that the basal stem cells of the olfactory epithelium were previously believed to be restricted to the production of olfactory cells. In contrast, Applicants discovered, in peripheral tissues, the existence of cells capable of generating dopaminergic neurons and oligodendrocytes, two cells types not recognized to be produced by these tissues. As evidenced by the cited art, prior to the present discovery, one skilled in the art was not motivated to determine the variety of neuronal or glial cell types that could be produced, despite the ease with which this could be performed. Without the recognition that peripheral tissues contained neural stem cells having such multipotency, there would have been no motivation to transplant isolated neural stem cells into the CNS of a mammal, as is recited by claim 49. In sum, new claim 49 is novel, non-obvious, and enabled.

Rejections under 35 U.S.C. §§ 102(a), 102(b), and 103(a)

Claims 31, 32, 34-36, 39, 40, and 43-45 stand rejected for anticipation by Sosnowski (Brain Res. 702: 37-48, 1995). Claims 31, 32, 35, 35, 37-39, 40, and 43-45 stand further rejected for anticipation by Schubert (Proc. Natl. Acad. Sci. USA 82: 7782-7786). Claims 31, 32, 35, 36, 39, 40, 43-45, and 48 stand rejected for anticipation by

Ronnett (U.S. Patent No. 5,318,907). The claims also stand rejected for obviousness in view of Shubert in view of Le Gal La Salle (Science 259:988-990) or Mayo (Int. J. Dev. Biol. 36:255-263) in view of Kaufman (Proc. Natl. Acad. Sci. USA 85:9606-9610, 1988). In order to expedite the prosecution of the present application, Applicants have canceled claims 31, 34-37, 39, 40, and 48. Applicants reserve the right, however, to prosecute these claims in a subsequently filed application. Claims 32, 33, 38, 41, and 42 now depend from claim 49. Claims 43-45 each recites a cell differentiated from the cell of claim 49. Each of these claims is new and non-obvious over the cited art for the reasons provided above for claim 49.

Conclusion

Enclosed is a petition to extend the period for replying for three months, to and including June 6, 2000. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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